



MLH1 gene

mutL homolog 1

Normal Function

The *MLH1* gene provides instructions for making a protein that plays an essential role in DNA repair. This protein helps fix mistakes that are made when DNA is copied (DNA replication) in preparation for cell division. The MLH1 protein joins with another protein called PMS2 (produced from the *PMS2* gene), to form a protein complex. This complex coordinates the activities of other proteins that repair mistakes made during DNA replication. The repairs are made by removing a section of DNA that contains mistakes and replacing the section with a corrected DNA sequence. The *MLH1* gene is a member of a set of genes known as the mismatch repair (MMR) genes.

Health Conditions Related to Genetic Changes

Lynch syndrome

About 50 percent of all cases of Lynch syndrome with an identified gene mutation are associated with inherited mutations in the *MLH1* gene. Several hundred *MLH1* gene mutations have been found in people with this condition. Lynch syndrome increases the risk of many types of cancer, particularly cancers of the colon (large intestine) and rectum, which are collectively referred to as colorectal cancer. People with Lynch syndrome also have an increased risk of cancers of the endometrium (lining of the uterus), ovaries, stomach, small intestine, liver, gallbladder duct, upper urinary tract, and brain.

MLH1 gene mutations involved in this condition prevent the production of the MLH1 protein or lead to an altered version of this protein that does not function properly. When the MLH1 protein is absent or nonfunctional, the number of DNA mistakes that are left unrepaired during cell division increases substantially. The errors accumulate as the cells continue to divide, which may cause the cells to function abnormally, increasing the risk of tumor formation in the colon or another part of the body.

Some mutations in the *MLH1* gene cause a variant of Lynch syndrome called Turcot syndrome. In addition to colorectal cancer, people with Turcot syndrome tend to develop a particular type of brain tumor called a glioblastoma.

Another variant of Lynch syndrome, called Muir-Torre syndrome, can also be caused by mutations in the *MLH1* gene. In addition to colorectal cancer, people with this condition have an increased risk of developing several uncommon skin tumors. These rare skin tumors include sebaceous adenomas and carcinomas, which occur in glands that produce an oily substance called sebum (sebaceous glands). Multiple

rapidly growing tumors called keratoacanthomas may also occur, usually on sun-exposed areas of skin.

ovarian cancer

Inherited changes in the *MLH1* gene increase the risk of developing ovarian cancer, as well as other types of cancer, as part of Lynch syndrome (described above). Women with Lynch syndrome have an 8 to 10 percent chance of developing ovarian cancer in their lifetimes, as compared with 1.6 percent in the general population.

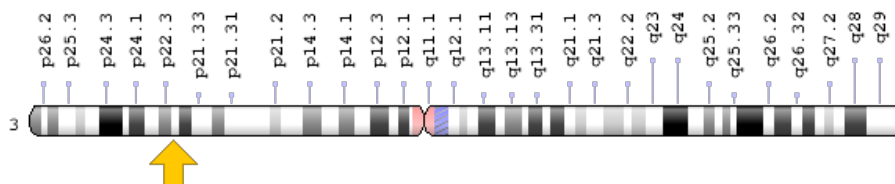
other cancers

While Lynch syndrome is associated with a mutation in one copy of the *MLH1* gene, very rarely, individuals in affected families inherit two *MLH1* gene mutations, one from each parent. Most often in these cases, the same mutation occurs in both copies of the gene (a homozygous mutation). People with a homozygous *MLH1* gene mutation have a syndrome distinct from Lynch syndrome. In addition to colorectal cancer, these individuals may develop cancers of the blood (leukemia or lymphoma). Some of these individuals will also develop characteristic features of a condition known as neurofibromatosis, including noncancerous tumors that grow along nerves (neurofibromas) and light brown patches of skin called café-au-lait spots. The onset of colon cancer in these individuals is extremely early, often occurring during childhood. This syndrome involving colon cancer, leukemia or lymphoma, and neurofibromatosis is sometimes called CoLoN.

Chromosomal Location

Cytogenetic Location: 3p22.2, which is the short (p) arm of chromosome 3 at position 22.2

Molecular Location: base pairs 36,993,350 to 37,050,846 on chromosome 3 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- COCA2
- FCC2
- hMLH1
- HNPCC
- HNPCC2
- MLH1_HUMAN
- mutL (E. coli) homolog 1 (colon cancer, nonpolyposis type 2)
- mutL homolog 1, colon cancer, nonpolyposis type 2 (E. coli)
- MutL protein homolog 1

Additional Information & Resources

Educational Resources

- American Medical Association and National Coalition for Health Professional Education in Genetics: Understand the Basics of Genetic Testing for Hereditary Colorectal Cancer
<http://www.nchpeg.org/documents/crc/Basics%20of%20genetic%20testing.pdf>
- Cancer Medicine (sixth edition, 2003): DNA Mismatch Repair Gene Defects and HNPCC
<https://www.ncbi.nlm.nih.gov/books/NBK12469/#A1595>
- Molecular Biology of the Cell (fourth edition, 2002): Defects in DNA Mismatch Repair Provide an Alternative Route to Colorectal Cancer
<https://www.ncbi.nlm.nih.gov/books/NBK26902/#A4345>

GeneReviews

- Lynch Syndrome
<https://www.ncbi.nlm.nih.gov/books/NBK1211>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28MLH1%5BTI%5D%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5BIa%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D>

OMIM

- MISMATCH REPAIR CANCER SYNDROME
<http://omim.org/entry/276300>
- MUIR-TORRE SYNDROME
<http://omim.org/entry/158320>
- MutL, E. COLI, HOMOLOG OF, 1
<http://omim.org/entry/120436>

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
<http://atlasgeneticsoncology.org/Genes/MLH1ID149ch3p21.html>
- ClinVar
<https://www.ncbi.nlm.nih.gov/clinvar?term=MLH1%5Bgene%5D>
- HGNC Gene Family: MutL homologs
<http://www.genenames.org/cgi-bin/genefamilies/set/1027>
- HGNC Gene Symbol Report
http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=7127
- NCBI Gene
<https://www.ncbi.nlm.nih.gov/gene/4292>
- UniProt
<http://www.uniprot.org/uniprot/P40692>

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<https://ghr.nlm.nih.gov/gene/MLH1>

Reviewed: October 2015
Published: March 21, 2017

Lister Hill National Center for Biomedical Communications
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